



(72) GILCHRIST, Eilidh, GB

(72) GILCHRIST, Thomas, GB

(71) GILTECH LIMITED, GB

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(54) **ALGINATE CONTENANT UNE COMPOSITION MICROBICIDE**

(54) **ALGINATE CONTAINING ANTIMICROBIAL COMPOSITION**

(57) L'invention porte sur une composition consistant en un mélange additionnel d'un alginat finement divisé (ou leurs sels ou dérivés) et d'un support également finement divisé. Cette composition résout les problèmes liés à l'application d'alginate en gélifiants sur des surfaces corporelles en empêchant la formation d'une pâte compacte occasionnant des irritations locales. Un mélange d'alginate de sodium et d'un support de verre hydrosoluble a la préférence. Eventuellement, alginat et son support peuvent présenter une taille de particules de moins de 150 .mu.m de diamètre et être présents selon un rapport allant de 20:80 à 80:20. La présence du support contribue à la gélification et favorise la cicatrisation des plaies.

(57) There is provided a composition comprising an admixture of a finely divided alginate (or a salt or derivative thereof) together with a finely divided carrier material. The composition overcomes the problems associated with applying gel-forming alginates to a body surface without formation of a clumpy paste that leads to local irritation. An admixture of sodium alginate and a water-soluble glass carrier material is preferred. Optionally, the alginate and carrier material each have a particle size of less than 150 .mu.m diameter and are present in a weight ratio of 20:80 to 80:20. The presence of the carrier aids even gel formation and also promotes wound healing.



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<b>(21) International Application Number:</b> PCT/GB97/00715 <b>(22) International Filing Date:</b> 13 March 1997 (13.03.97) <b>(30) Priority Data:</b> 9605247.7      13 March 1996 (13.03.96)      GB <b>(71) Applicant (for all designated States except US):</b> GILTECH LIMITED [GB/GB]; 9/12 North Harbour Industrial Estate, Ayr KA8 8AA (GB). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> GILCHRIST, Eilidh [GB/GB]; 11 Monkton Road, Prestwick, Ayrshire KA9 1AP (GB). GILCHRIST, Thomas [GB/GB]; The Lodge, 67 Midton Road, Ayr, Ayrshire KA7 2TW (GB). <b>(74) Agent:</b> MURGITROYD & COMPANY; 373 Scotland Street, Glasgow G5 8QA (US).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>  <b>(88) Date of publication of the international search report:</b> 23 October 1997 (23.10.97)
<b>(54) Title:</b> ALGINATE CONTAINING ANTIMICROBIAL COMPOSITION  <b>(57) Abstract</b>  <p>There is provided a composition comprising an admixture of a finely divided alginate (or a salt or derivative thereof) together with a finely divided carrier material. The composition overcomes the problems associated with applying gel-forming alginates to a body surface without formation of a clumpy paste that leads to local irritation. An admixture of sodium alginate and a water-soluble glass carrier material is preferred. Optionally, the alginate and carrier material each have a particle size of less than 150 <math>\mu</math>m diameter and are present in a weight ratio of 20:80 to 80:20. The presence of the carrier aids even gel formation and also promotes wound healing.</p>		

1                   **ALGINATE CONTAINING ANTIMICROBIAL COMPOSITION**

2  
3       The present invention relates to an anti-microbial  
4       composition for use in medical or veterinary  
5       applications.

6  
7       A wide variety of gels, creams, ointments, lotions etc  
8       are available for application to a body surface. The  
9       exact content of such compositions generally depends  
10      upon the purpose of application which may be, for  
11      example, to clean a body surface, to promote healing of  
12      any wound or injury, to prevent an exposed area of the  
13      body from drying out, to prevent infection etc. In  
14      certain circumstances the composition may include an  
15      active ingredient which is administered to the patient  
16      by application of the composition.

17  
18      One example of a commercially available gel is  
19      INTRASITE™ produced by Smith & Nephew Ltd. This  
20      hydrogel contains hydrated carboxymethylcellulose as  
21      its main ingredient, and is applied to wounds in gel  
22      form as a primary treatment in order to clean the  
23      exposed surface by aiding removal of cell debris, dirt  
24      etc. In addition to acting as a sloughing agent, the  
25      gel also keeps the wound from drying out, thereby

1 promoting healing.

2

3 Another example of a gel suitable for use on a wound  
4 dressing is described in EP-A-0586260 of Courtaulds  
5 Fibres Ltd. The gel disclosed is an alginate gel  
6 having an alginate content of 2 to 11 percent by  
7 weight.

8

9 Surgical dressings based on gel forming alginates have  
10 a significant contribution to make in wound management  
11 and are generally presented as preformed components of  
12 gels and pastes and as fibres of calcium or mixed  
13 calcium/sodium salts.

14

15 In alginate-based surgical dressings the starting raw  
16 material is usually the sodium salt which is supplied  
17 by the alginate producer as a dry powder. Attempts to  
18 utilise alginate as topical powders for direct  
19 application to wounds have not proved successful. This  
20 is because the irregularly dispersed powder does not  
21 wet easily and clumping occurs leading to clusters of  
22 dry particles which can be sites of local irritation.  
23 There is incomplete gelling as a result and the desired  
24 sealing of the wound with a smooth hydrogel coating is  
25 not achieved.

26

27 It has now been found that an admixture of finely  
28 divided alginate (the term "alginate" being used herein  
29 to refer to alginates, the derivatives and salts  
30 thereof) and a different finely divided carrier  
31 material can be applied to wounds or other moist body  
32 surfaces. The combination of the carrier material  
33 together with the alginate facilitates the formation of  
34 an even gel coating and the avoidance of clumping.

35

36 Suitable carrier materials include proteins (eg

1 casein), salts (eg sodium, zinc, calcium, magnesium and  
2 potassium salts) and water-soluble glass. Desirably  
3 the carrier material is water-soluble or water  
4 miscible.

5  
6 More surprisingly, it has been found that the  
7 alginate/carrier combination acts in synergy to promote  
8 healing and cell growth. For example, in animal  
9 implant studies which compared alginate powder alone  
10 and a water-soluble glass powder alone with a blend of  
11 both, it was demonstrated that tissue response was  
12 clearly better for the mixed powders than that seen  
13 with either material on its own. In particular at 14  
14 days after implantation there was little evidence of  
15 the inflammatory cells which were residually present in  
16 the single material implant sites.

17  
18 Viewed from one aspect the present invention provides  
19 an admixture of alginate or a derivative or salt  
20 thereof together with a carrier material. Generally  
21 both main components are finely divided, i.e. are in  
22 powder, particulate or granular form.

23  
24 Desirably the finely divided alginate and carrier  
25 material components may each have a diameter size of  
26 150µm or less. Preferably the mode particle size for  
27 either component is 100µm or less. More preferably the  
28 mode particle size for either component is 60µm or  
29 less, for example 30-60µm.

30  
31 The two components may be combined together in any  
32 suitable mixture. Suitable mixtures include those  
33 having a ratio of from 20:80 to 80:20 (% by weight) of  
34 alginate:carrier. Preferred mixtures include those  
35 having an alginate:carrier ratio in the range of 20:80  
36 to 50:50, preferably 20:80 to 30:70, for example 25:75.

1 Water-soluble glasses are a preferred form of carrier  
2 material. The use of glasses which can dissolve in  
3 water and body fluid and which are applied internally  
4 of the body are well-known. These glasses are formed  
5 from phosphorus pentoxide and may be modified to  
6 dissolve over a period of minutes, months or even  
7 years, as required. To date, such glasses have been  
8 used, in medicine, for the controlled release of a  
9 number of agents, for example, drugs, hormones and  
10 trace elements, but in each case the glass has been  
11 applied internally of the body to allow the agent to  
12 leach out into the body's circulatory system.

13  
14 It is known that certain glasses, in which the usual  
15 glass former, silicon dioxide, of traditional glasses  
16 is replaced with phosphorus pentoxide as the glass  
17 former, are soluble in water and body fluids. The rate  
18 of dissolution is controlled largely by the addition of  
19 glass modifiers such as calcium and magnesium oxide.  
20 In simple terms, the greater the concentration of the  
21 modifier the slower is the rate of dissolution. The  
22 rates of dissolution which can be imparted to the  
23 glasses may range from minutes to months or even to  
24 several years. It is known to include in such  
25 compositions quantities of trace elements such as  
26 copper, cobalt and selenium which will be released from  
27 the glass as it slowly dissolves over the selected  
28 period of time.

29  
30 The use of water-soluble glasses has been described for  
31 a variety of purposes in the literature. For example,  
32 UK Patent Specifications numbers 1,565,906, 2,079,152,  
33 2,077,585 and 2,146,531 describe the gradual  
34 dissolution of the glasses as providing a means of  
35 controlled release of drugs, hormones, fungicides,  
36 insecticides, spermicides and other agents with which

1 the glasses have been impregnated. The glasses are  
2 used for example in the form of an implant or bolus.

3  
4 UK Patent Specification number 2,030,559 describes the  
5 use of selenium-impregnated water-soluble glass for  
6 providing controlled release of the selenium as a trace  
7 element into cattle and sheep, the glass being applied  
8 as a subcutaneous insert. UK Patent Specification  
9 number 2,037,735 also describes a subcutaneous implant  
10 of water-soluble glass, and in this case the glass is  
11 impregnated with copper; minor quantities of trace  
12 elements such as boron, arsenic, iodine, manganese,  
13 chromium, silver, gold and gallium may also be  
14 included.

15  
16 Water-soluble glass has also been proposed for use in  
17 prosthetics, for example in UK Patent Specification  
18 number 2,099,702, and for use in anticorrosive paints,  
19 as described in UK Patent Specification number  
20 2,062,612. Further the literature provides for the use  
21 of such glasses in the controlled release of ferrous  
22 and ferric ions into the human or animal body by  
23 ingestion or implantation of the glass (UK Patent  
24 Specification number 2,081,703), and for the use of  
25 glasses in the controlled release of ions such as  
26 lithium, sodium, potassium, caesium, rubidium,  
27 polyphosphate, calcium and aluminium to patients by  
28 inclusion of the glass in a drip feed line (UK Patent  
29 Specification number 2,057,420).

30  
31 WO-A-89/01793 relates to apparatus for antimicrobial  
32 use in passage of fluid to or from a living body, the  
33 apparatus comprising a conduit for insertion into the  
34 body, a reservoir for fluid and a connector member for  
35 connecting said conduit to said reservoir external of  
36 the body, wherein said connector member includes a

1 water-soluble glass impregnated with elemental silver  
2 or a compound of silver, said water-soluble glass  
3 defining at least a part of a passageway for fluid to  
4 flow between the reservoir and the conduit.  
5  
6 Desirably the water-soluble glass is a silver  
7 containing water-soluble glass. Advantageously the  
8 silver content will be introduced into the glass  
9 composition in the form of silver orthophosphate.  
10  
11 Suitable glasses include, for example, the ARGLAES™  
12 glass of Giltech Limited.  
13  
14 Preferably, said glass is adapted by the use of glass  
15 modifiers to give a sustained release of silver ions  
16 over a set period.  
17  
18 In one embodiment the water-soluble glass comprises an  
19 alkali metal oxide  $M_2O$ , an alkaline earth oxide  $MO$ ,  
20 phosphorus pentoxide  $P_2O_5$ , and silver oxide ( $Ag_2O$ ) or  
21 silver orthophosphate ( $Ag_3PO_4$ ).  
22  
23 Most preferably, said glass contains not more than 40  
24 mole %  $M_2O$  or  $MO$ , not less than 10 mole %  $M_2O$  or  $MO$ , and  
25 not more than 50 mole % nor less than 38 mole %  
26 phosphorus pentoxide, with the inclusion of 0.05 to 5.0  
27 mole % silver oxide or orthophosphate.  
28  
29 Said alkali metal oxide may be sodium oxide ( $Na_2O$ ),  
30 potassium ( $K_2O$ ) or a mixture thereof; and said alkaline  
31 earth oxide may be calcium oxide ( $CaO$ ), magnesium oxide  
32 ( $MgO$ ), zinc oxide ( $ZnO$ ) or a mixture thereof.  
33  
34 The glass may also contain less than 5 mole % silicon  
35 dioxide ( $SiO_2$ ), boric oxide ( $B_2O_3$ ), sulphate ion ( $SO_4^{2-}$ ),  
36 a halide ion, copper oxide ( $CuO$ ) or a mixture thereof.



1 Typically the soluble glasses used in this invention  
2 comprise phosphorus pentoxide ( $P_2O_5$ ) as the principal  
3 glass-former, together with any one or more  
4 glass-modifying non-toxic materials such as sodium  
5 oxide ( $Na_2O$ ), potassium oxide ( $K_2O$ ), magnesium oxide  
6 ( $MgO$ ), zinc oxide ( $ZnO$ ) and calcium oxide ( $CaO$ ). The  
7 rate at which the silver-release glass dissolves in  
8 fluids is determined by the glass composition,  
9 generally by the ratio of glass-modifier to  
10 glass-former and by the relative proportions of the  
11 glass-modifiers in the glass. By suitable adjustment  
12 of the glass composition, the dissolution rates in  
13 water at  $38^\circ C$  ranging from substantially zero to  
14  $25\text{mg}/\text{cm}^2/\text{hour}$  or more can be designed. However, the  
15 most desirable dissolution rate  $R$  of the glass is  
16 between  $0.01$  and  $2.0\text{mg}/\text{cm}^2/\text{hour}$ . The water-soluble  
17 glass is preferably a phosphate glass, and the silver  
18 may advantageously be introduced during manufacture as  
19 silver orthophosphate ( $Ag_3PO_4$ ). The content of silver  
20 and other constituents in the glass can vary in  
21 accordance with conditions of use and desired rates of  
22 release, the content of silver generally being up to 5  
23 mole %. While we are following convention in  
24 describing the composition of the glass in terms of the  
25 mole % of oxides, of halides and of sulphate ions, this  
26 is not intended to imply that such chemical species are  
27 present in the glass nor that they are used for the  
28 batch for the preparation of the glass.  
29  
30 The optimum rate of release of silver ions into an  
31 aqueous environment may be selected by circumstances  
32 and particularly by the specific function of the  
33 released silver. The invention provides a means of  
34 delivering silver ions to an aqueous medium at a rate  
35 which will maintain a concentration of silver ions in  
36 said aqueous medium of not less than 0.01 parts per

1 million and not greater than 10 parts per million. In  
2 some cases, the required rate of release may be such  
3 that all of the silver added to the system is released  
4 in a short period of hours or days and in other  
5 applications it may be that the total silver be  
6 released slowly at a substantially uniform rate over a  
7 period extending to months or even years. In  
8 particular cases there may be additional requirements,  
9 for example it may be desirable that no residue remains  
10 after the source of the silver ions is exhausted or, in  
11 other cases, where the silver is made available it will  
12 be desirable that any materials, other than the silver  
13 itself, which are simultaneously released should be  
14 physiologically harmless. In yet other cases, it may  
15 be necessary to ensure that the pH of the resulting  
16 solution does not fall outside defined limits.

17  
18 The glass may be formed by a number of methods. It may  
19 simply be cast by conventional or centrifugal  
20 procedures, or it may be prepared via one or more  
21 stages of rod, fibre or tube drawing. Other  
22 preparation techniques include foamed glass. Following  
23 glass formation it will be comminuted into finely  
24 divided form.

25  
26 With regard to the alginate component, derivatives and  
27 salts of alginates are acceptable for use in the  
28 present invention. Sodium and calcium salts of  
29 alginate or a combination of these two salts is  
30 preferred. Sodium alginate is especially preferred.

31  
32 In one preferred embodiment, the composition of the  
33 present invention is an admixture of sodium alginate  
34 powder and water soluble glass (eg ARGLAES™ of Giltech  
35 Limited) in a ratio of alginate:glass of 25:75 by  
36 weight. Preferably, the water soluble glass releases

1 calcium ions as it dissolves. The calcium ions  
2 displace some of the sodium ions in the sodium alginate  
3 thus forming calcium alginate. The presence of calcium  
4 alginate stabilises the alginate gel.

5  
6 The composition may be pre-mixed, or alternatively the  
7 alginate may be kept separately from the carrier  
8 material and the ingredients admixed together  
9 immediately prior to use. This enables a particular  
10 blend to be formulated to suit the wound or condition  
11 in question.

12  
13 Optionally, the composition of the present invention  
14 may contain an active ingredient. The term "active  
15 ingredient" is used herein to refer to any agent which  
16 affects the metabolism or any metabolic or cellular  
17 process of the patient (including growth factors and  
18 living cells), promotes healing, combats infection,  
19 hypergranulation or inflammation. Antibiotics and  
20 other anti-bacterial agents, steroids, painkillers etc  
21 are all suitable. Optionally, the active ingredient  
22 may be in delay-release or controlled-release form.

23  
24 The composition of the present invention may be used to  
25 clean a body surface, to promote healing of a wound or  
26 injury, to prevent an exposed area of the body from  
27 drying out or to prevent infection.

28  
29 In a further aspect the present invention provides a  
30 method of treating the human or non-human (preferably  
31 mammalian) animal body, said method comprising applying  
32 a finely divided admixture of an alginate (a derivative  
33 or salt thereof) and a carrier material, such as a  
34 (preferably silver-containing) water-soluble glass, to  
35 a body surface, for example to a wound.

36

1 The invention will now be further described with  
2 reference to the figures:

3

4 Fig 1 illustrates a mass of inflammatory cells at the  
5 site of implantation of a composition of just silver  
6 ion releasing glass, 7 days after implantation.

7

8 Fig 2 illustrates a mass of inflammatory cells and the  
9 damage to the muscle bed at the site of implantation of  
10 alginate, 2 days after implantation.

11

12 Fig 3 is a higher magnification of the same tissue  
13 block as in Fig 2.

14

15 Fig 4 illustrates a mass of inflammatory cells sitting  
16 on and infiltrating the muscle bed at the site of  
17 implantation of a composition of just alginate, 7 days  
18 after implantation.

19

20 Fig 5 is a higher magnification of the same tissue  
21 block as in Fig 4.

22

23 Fig 6 illustrates a number of inflammatory cells and  
24 the broken up muscle bed at the site of implantation of  
25 a composition of alginate and a water soluble glass  
26 carrier, 2 days after implantation.

27

28 Fig 7 illustrates a number of inflammatory cells and a  
29 normal muscle bed at the site of implantation of a  
30 composition of alginate and a water soluble glass  
31 carrier, 7 days after implantation.

32

33 and with reference to the following, non-limiting,  
34 examples.

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11

1     EXAMPLE 1

2

3     To determine the tissue response to the powdered  
4     biomaterials using a rat model and further to determine  
5     whether combining the two materials had a significant  
6     effect on the response.

7

8     Materials

9

10	CRG/silver powder [D301893 Ag 3 mole%]	..	CRG/Ag
11	Alginate powder [lot No 544831]	.....	Alginate
12	CRG/silver powder and		
13	Alginate powder [50:50] mix	.....	Alginate/CRG/Ag

14

15     The silver containing controlled release glass (herein  
16     referred to as "CRG/silver") had the following

17	composition	Na <sub>2</sub> O	27.5 mole %
18		CaO	22 mole %
19		Ag <sub>2</sub> O	3.5 mole %
20		P <sub>2</sub> O <sub>5</sub>	47 mole %

21

22     The silver content of the glass was added in the form  
23     of silver orthophosphate, but is expressed as "silver  
24     oxide" according to convention. 100% of the glass  
25     particles had a diameter of less than 53µm.

26

27     The alginate used was a pure sodium alginate salt,  
28     commercially available as Manucol™ LXX of Kelco  
29     International Limited, United Kingdom. The volume mode  
30     particle size of the sodium alginate is 41.46µm and  
31     99.4% of the particles had a diameter of less than  
32     49.99µm.

33

34     All materials were supplied in powder form. The  
35     Alginate/Ag mix was prepared by hand. The materials  
36     were not sterilised before implantation. No infection

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12

1 problems were encountered during the procedures.

2

3 Method

4

5 Adult, black and white hooded rats of the Lister strain  
6 (approximately 200g) were used for all procedures.  
7 Appropriate surgical methods were employed by  
8 experienced personnel, and all procedures were carried  
9 out as detailed in UK Home Office licence No  
10 PP140/01099.

11

12 A small incision was made above the lumbar sacral  
13 vertebrae, and the muscle bed on either side of this  
14 incision was exposed by blunt dissection. A pocket was  
15 created in the muscle fibres and approximately 2mg of  
16 the powdered material was carefully placed into this  
17 pocket. Inevitably, some powder material was deposited  
18 on the muscle bed surface and contacted subcutaneous  
19 tissue. Animals were sacrificed at 2, 7 and 14 days  
20 using a schedule one method.

21

22 Following sacrifice, the tissue was examined for any  
23 obvious signs of inflammation, and a block of  
24 tissue/muscle containing the implant site was removed.  
25 The block was immediately frozen, sectioned on a  
26 cryostat microtome to produce sections 7µm thin and  
27 stained using haematoxylin and eosin. The sections  
28 were examined by light microscopy.

29

30 Results

31

32 CRG/Aq

33

34 2 days

35

36 There were no signs of gross inflammation when the

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13

1 animals were sacrificed. Following staining the site  
2 could be seen to be heavily inflamed. The muscle was  
3 widely infiltrated with neutrophils, and the muscle  
4 fibres were disrupted. A black particulate material  
5 (believed to be an Ag/Ag complex) was evident and  
6 neutrophils were very densely packed around these  
7 particles.

8

9 7 days

10

11 Although the muscle site appeared clean, there was a  
12 large volume of clear exudate present at each implant  
13 site. The exudate had produced a swelling under the  
14 skin at the site of the implantation. Following  
15 staining, a mass of inflammatory cells were seen to be  
16 present at the site (Fig 1). These cells appeared to  
17 be predominantly neutrophils. The muscle fibres  
18 appeared normal and there was no evidence of necrotic  
19 tissue, though there remained some inflammatory  
20 infiltration. Particulate matter was present though  
21 not black in this case. It looked more like a  
22 degrading glass. The silver could not be detected at  
23 this time.

24

25 14 days

26

27 The exudate and associated swelling had subsided by  
28 this time, however when the site was exposed there was  
29 evidence of tissue damage (believed to be necrosis) on  
30 the muscle bed and in contiguous subcutaneous tissue.  
31 Following staining extensive inflammation was apparent,  
32 and there was evidence of necrotic tissue. However,  
33 only a small area was affected. Some dark, particulate  
34 material was also evident. This may be a silver  
35 complex. Degrading glass material is clearly present  
36 at the site.

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14

1     Alginate

2

3     2 days

4

5     No gross signs of inflammation were present when the  
6     animals were sacrificed. However, the alginate was  
7     clearly visible on and around the implant site as a  
8     "messy" gel. Following staining, large numbers of  
9     inflammatory cells could be seen (Fig 2), the muscle  
10    bed was damaged and the muscle fibres were disturbed  
11    and infiltrated with these cells. This was possibly  
12    due to the presence of small particulate material  
13    invading the muscle and stimulating an inflammatory  
14    response. However, there was no evidence of necrotic  
15    response.

16

17    Fig 3 shows a higher magnification of the response from  
18    the same tissue block as Fig 2. Inflammatory cells can  
19    be seen invading the muscle fibres. Most of the pink  
20    stained material visible was alginate, clearly well  
21    dispersed. Muscle fibres (also stained pink) could be  
22    seen in the top right corner. Alginate could be seen,  
23    stained pink.

24

25    7 days

26

27    No signs of gross inflammation were evident when the  
28    animals were sacrificed. No alginate could be seen at  
29    this time, and the muscle bed appeared clean.  
30    Following staining (Fig 4), large numbers of  
31    inflammatory cells could be seen remaining at the  
32    implant site. However, there was very little evidence  
33    of alginate remaining at the site even when the site  
34    was observed under higher magnification (Fig 5). The  
35    result was very similar to that observed with the Ag at  
36    7 days although in this case there was no exudate



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15

1 build-up.

2

3 14 days

4

5 No sign of gross inflammation was present when the  
6 animal was sacrificed. Following staining, large  
7 numbers of inflammatory cells were evident at the  
8 implant site. There was some evidence of alginate  
9 remaining at the site, but only very little. There was  
10 no evidence of necrosis or damage to the tissue.

11

12 Alginate/CRG/Ag

13

14 2 days

15

16 There were no gross signs of inflammation when the  
17 animals were sacrificed, and the muscle bed appeared  
18 clean. Following staining (Fig 6), the muscle fibres  
19 could be seen to be disturbed and the muscle bed to be  
20 broken up. This was likely to be due to the  
21 particulate matter stimulating infiltration of  
22 inflammatory cells. However, there appeared to be  
23 fewer inflammatory cells at the implant site or  
24 infiltrating the muscle than was evident when the  
25 materials were examined alone. There was only little  
26 evidence of particulate material remaining at the site.  
27 Once again, this appeared to be a degrading glass.

28

29 7 days

30

31 There were no gross signs of inflammation when the  
32 animals were sacrificed. Following staining (Fig 7),  
33 large numbers of inflammatory cells could be seen at  
34 the implant site. There was some particulate material  
35 present, though it was not clear what this was. The  
36 response was similar to that seen at 2 days. However,

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16

1 the muscle bed now seems normal with the muscle fibres  
2 intact. The result was very similar to that seen with  
3 the materials examined alone at the same time period.

4  
5 14 days

6  
7 There were no signs of gross inflammation at the  
8 implant site following sacrifice. Staining showed a  
9 clean muscle block with only little evidence of  
10 inflammatory cells. The response at 14 days with the  
11 mixed materials, was clearly better than that seen with  
12 either material when examined alone. No evidence of  
13 any particulate material could be found at this time.

14  
15 Conclusion

16  
17 The majority of inflammation that is seen with these  
18 samples can probably be attributed to:

- 19  
20 a. the surgical procedure itself; we are examining  
21 the tissue response within the normal wound  
22 healing time;  
23  
24 b. the fact that the material has been applied in  
25 power/particulate form; this will inevitably lead  
26 to a more extensive inflammation.

27  
28 Nevertheless, differences have been noted in the  
29 responses to the materials examined. Silver containing  
30 CRG gave rise to a considerable exudate which was at  
31 its most severe, certainly most obvious at 7 days.  
32 This exudate was clearly visible under the skin as a  
33 lump, and the area was obviously painful to the animal.  
34 On sacrifice the exudate was revealed as a clear,  
35 subcutaneous fluid. At 14 days the exudate had  
36 subsided, although there remained a "sore" on the skin.

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17

1 When exposed, the implant site, particularly the muscle  
2 bed surface and the subcutaneous tissue in contact with  
3 the implant site, was damaged. Histology showed that  
4 there was some evidence of necrotic tissue, though this  
5 was minimal.

6  
7 The alginate alone produced a "messy" gel on the muscle  
8 surface at 2 days, but subsequent time periods showed a  
9 clean muscle bed. Inflammation was associated with the  
10 implant site at all time periods. However, there was  
11 no evidence of damage or necrotic tissue. Although the  
12 alginate is clearly dissolving, traces of alginate  
13 could still be found at the site for 14 days.

14  
15 The alginate/silver mix seemed to attract less cells to  
16 the site at 2 days. At 7 days the response was fairly  
17 similar to that seen with the samples examined alone  
18 and no exudate was formed. However, after 14 days the  
19 healing response seemed much accelerated with this  
20 sample. Clean, normal muscle tissue was observed, with  
21 little evidence of inflammatory infiltration.

22  
23 EXAMPLE 2

24  
25 Materials examined:

26  
27 CRG/Ag powder  
28 Alginate powder  
29 Alginate/CRG/Ag powder

30  
31 All the samples were implanted as powders.

32  
33 Adult, black and white hooded Lister rats  
34 (approximately 200g) were used.

35  
36 A small incision was made above the lumbar sacral

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18

1 vertebrae. A pocket was created in the muscle fibres  
2 and approximately 5mg of the material was placed into  
3 the pocket. The wound was sutured with silk.  
4

5 Two samples of each material were placed in each animal  
6 and two animals used for each time period. Animals  
7 were sacrificed at two and seven days.  
8

9 At sacrifice the tissue was examined for any obvious  
10 signs of inflammation and a block of muscle containing  
11 the implant site removed. The block was frozen,  
12 sectioned on a microtome at 7 microns and stained by  
13 haematoxylin and eosin.  
14

15 CRG/Ag Powder  
16

17 2 days  
18

19 There were no gross signs of inflammation when the  
20 animal was sacrificed. Following staining, the site  
21 could be seen to be heavily inflamed. The muscle was  
22 widely infiltrated with neutrophils, and the muscle  
23 fibres disrupted. A black particulate material (Ag/Ag  
24 complex) was in evidence and neutrophils were very  
25 densely packed around these particles.  
26

27 7 days  
28

29 Although the muscle site looked clean, there was a  
30 large volume of clear exudate present with each animal.  
31 The exudate had produced a swelling under the skin at  
32 the site of the implant. Following staining, a huge  
33 mass of inflammatory cells were present at the implant  
34 site. These cells appear to be predominantly  
35 neutrophils. The muscle fibres looked normal, though  
36 there remained a considerably inflammatory cell

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19

1 infiltration. There was some particulate matter  
2 present, though not black in this case. It looked more  
3 like a degrading glass.

4  
5 Alginate powder

6  
7 2 days

8  
9 No gross signs of inflammation when the animal was  
10 sacrificed, though the alginate was clearly visible on  
11 and around the implant site, as a "messy" gel.  
12 Following staining, large numbers of inflammatory cells  
13 could be seen and the muscle fibres were disturbed and  
14 infiltrated with these cells. Alginate could be seen,  
15 stained pink.

16  
17 7 days

18  
19 No gross signs of inflammation when the animal was  
20 sacrificed. No sign of alginate at this time. Muscle  
21 bed looked very clean. Following staining, large  
22 numbers of inflammatory cells could be seen remaining  
23 at the implant site, however, there was very little  
24 evidence of alginate remaining at the site. The result  
25 was similar to that observed with CRG/Ag at 7 days,  
26 although in this case there was no exudate build up.

27  
28 Alginate/CRG/Ag

29  
30 2 days

31  
32 No gross signs of inflammation when the animal was  
33 sacrificed. The muscle bed was clean. Following  
34 staining, the muscle fibres could be seen to be broken  
35 up, however, there were less numbers of inflammatory  
36 cells at the implant site or infiltrating the muscle.

1 There was only little evidence of particulate material  
2 remaining at the site. Again this looked like a  
3 degrading glass.

4  
5 7 days

6  
7 No gross inflammation when the animal was sacrificed.  
8 Following staining large numbers of inflammatory cells  
9 could be seen at the site of implantation. Again there  
10 was some particulate material present (degrading  
11 glass). The muscle fibres were intact and normal.

12  
13 EXAMPLE 3

14  
15 Method

16 Other powders have also been combined with alginate to  
17 establish whether a) these combinations also formed a  
18 gel and b) if any such gel was tacky.

19  
20 The powders tried were casein, sodium chloride, zinc  
21 oxide, sodium borate, magnesium sulphate, magnesium  
22 chloride, calcium tetraborate and potassium iodide.

23  
24 Each powder was admixed individually with sodium  
25 alginate (Manuacol™ LXX) in a ratio of 3:1. The  
26 admixture was then applied to a damp simulated wound,  
27 covered with a dressing and left for 48 hours.

28  
29 Results

30 Admixtures with casein, sodium chloride, magnesium  
31 sulphite, magnesium chloride and potassium iodide  
32 formed sticky but "lump free" gels.

33  
34 Admixtures with zinc oxide and calcium tetraborate did  
35 not appear to wet out at all.

36

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21

- 1 The admixture with sodium borate did wet out
- 2 adequately, but formed a rubbery coating on the
- 3 simulated wound which did not stick to the dressing.

1     **CLAIMS**

2

3     1.    A composition comprising an admixture of finely  
4           divided alginate and a finely divided carrier  
5           material.

6

7     2.    An admixture as claimed in Claim 1, wherein the  
8           ratio of alginate:carrier material is in the range  
9           20:80 to 80:20 by weight.

10

11    3.    An admixture as claimed in Claim 2, wherein the  
12          ratio of alginate:carrier material is 25:75 by  
13          weight.

14

15    4.    A composition as claimed in any of the preceding  
16          Claims, wherein the carrier material is a water  
17          soluble glass.

18

19    5.    A composition as claimed in Claim 4, wherein said  
20          water soluble glass releases silver ions during  
21          dissolution.

22

23    6.    A composition as claimed in either one of Claims 4  
24          and 5, wherein said water soluble glass releases  
25          calcium ions during dissolution.

26

27    7.    A composition as claimed in any one of the  
28          preceding Claims, wherein the alginate is sodium  
29          alginate, calcium alginate or a mixture thereof.

30

31    8.    A composition as claimed in Claim 7, wherein the  
32          alginate is sodium alginate.

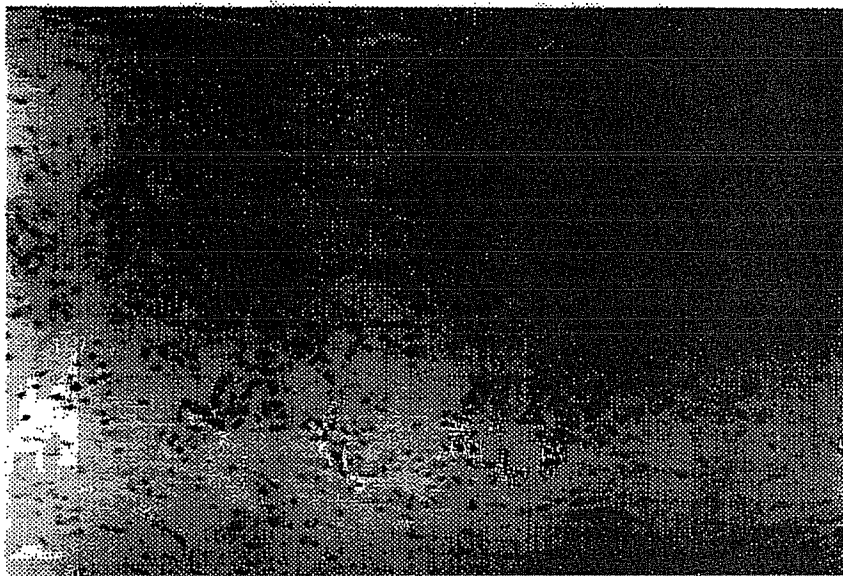
33

34    9.    A composition as claimed in any one of the  
35          preceding Claims, wherein said finely divided  
36          alginate has a particle diameter of 150  $\mu\text{m}$  or

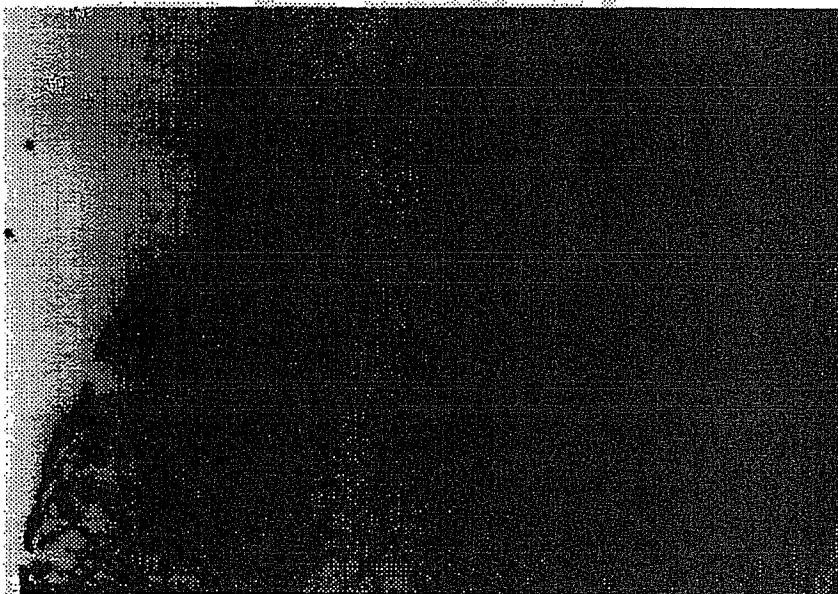


- 1           less.  
2
- 3       10. A composition as claimed in any one of the  
4           preceding Claims, wherein said finely divided  
5           carrier material has a particle diameter of 150  $\mu\text{m}$   
6           or less.  
7
- 8       11. A composition as claimed in any one of the  
9           preceding Claims, wherein said alginate and said  
10          carrier material each have a mode particle size of  
11          60  $\mu\text{m}$  or less.  
12
- 13      12. A composition as claimed in any one of the  
14          preceding Claims, said composition comprising  
15          75 parts by weight of a finely divided calcium ion  
16          releasing water soluble glass and 25 parts by  
17          weight of finely divided sodium alginate, said  
18          glass and said alginate each having a mode  
19          particle size of 60  $\mu\text{m}$  or less.  
20
- 21      13. A method of treatment of a human or non-human  
22          animal body, said method comprising applying to a  
23          surface of said body a composition as claimed in  
24          any one of Claims 1 to 12.  
25
- 26      14. Use of a composition as claimed in any one of  
27          Claims 1 to 12 to clean a body surface, to promote  
28          healing of a wound or injury, to prevent an  
29          exposed area of the body from drying out or to  
30          prevent infection.

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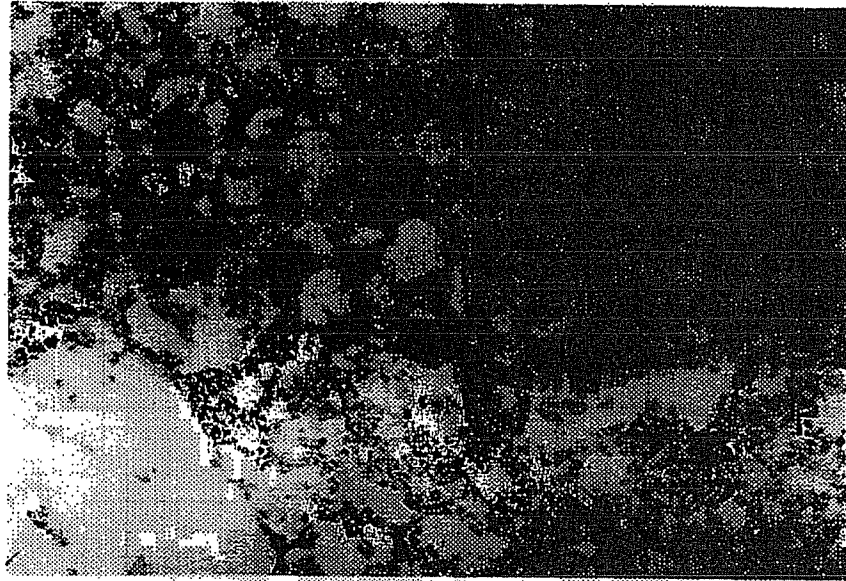


*Fig. 1*

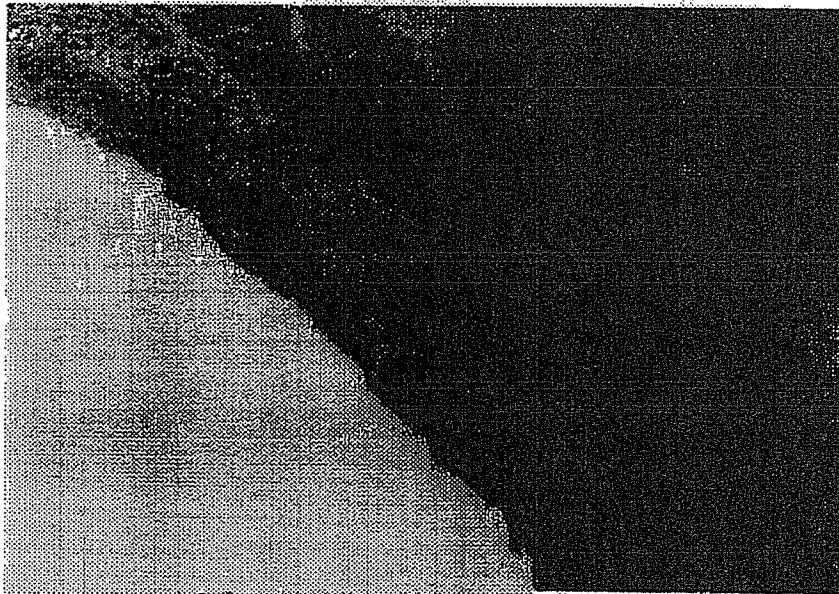


*Fig. 2*

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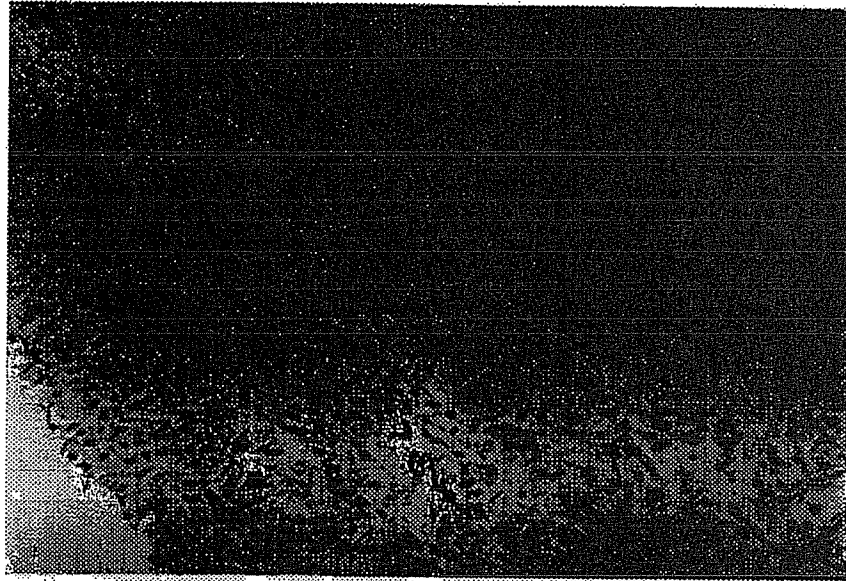


*Fig. 3*



*Fig. 4*

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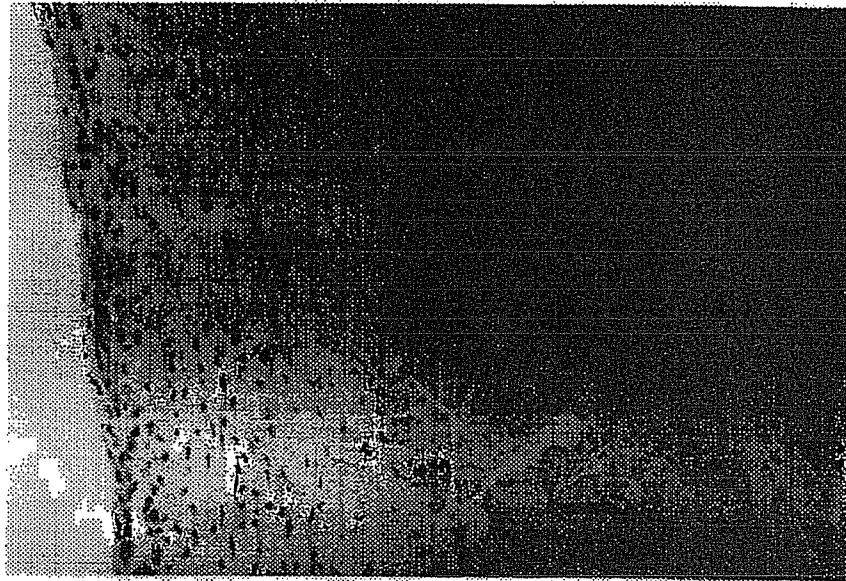


*Fig. 5*



*Fig. 6*

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*Fig. 7*